IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC., Plaintiff, v. MSN LABORATORIES PRIVATE LIMITED and MSN PHARMACEUTICALS, INC, Defendants.	C.A. No. 19-2017 (RGA) (SRF) (Consolidated)

DEFENDANTS' OPENING POST-TRIAL BRIEF ON INVALIDITY

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I. INTRODUCTION

Plaintiff asserts claim 5 of U.S Patent No. 7,579,473 ("the '473 patent"). The trial showed by clear and convincing evidence that claim 5 is invalid because it would have been obvious to a person of skill in the art ("POSA") as of the September 26, 2003 priority date.

Claim 5 recites the compound cabozantinib or its pharmaceutically acceptable salt. Cabozantinib is a compound that inhibits certain tyrosine kinases, including c-Met. The evidence presented at trial showed that a POSA would have been motivated to develop a c-Met inhibitor for treating cancers such as renal cancer and would have selected a lead compound for further development from the Kirin Publication—the *only* prior art reference that disclosed specific exemplified potent small molecule c-Met inhibitors. Plaintiff's experts conceded these points during trial. Clear and convincing evidence further showed that Kirin Example 5 would have been an obvious lead compound and that a POSA would have been motivated to prepare cabozantinib by introducing one simple modification, i.e., adding a geminal cyclopropyl group to both improve the metabolic stability of the compound and to increase the potential for irreversible inhibition of c-Met. Further, a POSA would have reasonably expected that the geminal cyclopropyl analog of Kirin Example 5 (i.e., cabozantinib) would inhibit c-Met.

For the reasons presented at trial and below, the Court should invalidate claim 5 and enter judgment for MSN and against Plaintiff.

II. LEGAL STANDARD

A patent claim is invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Whether a patent claim is invalid for

obviousness is a question of law based on four underlying questions of fact: (a) the level of ordinary skill in the pertinent art; (b) the scope and content of the prior art; (c) the differences between the prior art and the claims at issue; and (d) secondary considerations, which are also known as objective indicia of nonobviousness. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

The obviousness analysis requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)). The Supreme Court held that the Federal Circuit's prior requirement for some teaching, suggestion, or motivation in the art to combine references forming the basis for an obviousness contention was too rigid and propounded an "expansive and flexible approach" based on the principles laid down in *Graham*. *KSR*, 550 U.S. at 415; *see also Senju Pharm. Co. Ltd. v. Apotex Inc.*, 836 F. Supp. 2d 196, 208 (D. Del. 2011) ("The Supreme Court has emphasized the need for courts to value 'common sense' over 'rigid preventative rules.'").

In general, a claim is invalid for obviousness if "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention," and "would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007).

While obviousness must be shown by clear and convincing evidence, it is judged under "an expansive and flexible approach." *KSR*, 550 U.S. at 415. Under this framework, there is no requirement "that the motivation be the *best* option, only that it be a *suitable* option from which

the prior art did not teach away." *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014) (emphasis in the original).

"Obviousness does not require absolute predictability of success," but rather, "[a]ll that is required is a reasonable expectation of success" in making the invention. *Medichem, SA v. Rolabo, SL*, 437 F.3d 1157, 1165 (Fed. Cir. 2006); *see also In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Obviousness does not require absolute predictability. Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness."). Thus, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364. "When the prior art provides the means of making the invention and predicts the results, and the patentee merely verifies the expectation through 'routine testing,' the claims are obvious." *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 368 (D. Del. 2009) (citing *Pfizer*, 480 F.3d at 1367).

Whether a new chemical compound would have been obvious over prior art involves two steps evaluating: 1) whether a chemist of ordinary skill would have selected the prior art compound as a lead compound for development, and 2) whether the prior art would have provided a motivation to modify the lead compound to make the claimed compound with a reasonable expectation of success. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012).

The lead compound analysis "must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *see also Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). Rather, the analysis "requires the challenger to demonstrate by clear and convincing evidence that that one of ordinary skill in the art would have had a reason to select a proposed lead

compound or compounds over other compounds in the prior art." *Daiichi Sankyo*, 619 F.3d at 1354. For example, the selection of a known compound as a lead would be obvious if it is one of the more potent compounds out of a finite number identified in the prior art that is ripe for further experimentation. *See Altana Pharma*, 566 F.3d at 1007–09.

The motivation to modify the lead compound "may come from any number of sources and need not necessarily be explicit in the prior art." *Otsuka*, 678 F.3d at 1292. The "pertinent properties guide the analysis" in this step as well. *Id.* In other words, "[t]he 'reason or motivation' need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990)).

Secondary considerations, or objective indicia, such as "commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *KSR*, 550 U.S. at 406 (quoting *Graham*, 383 U.S. at 17–18).

III. ARGUMENT

A. Claim 5 Of The '473 Patent Is Invalid Because It Would Have Been Obvious.

Claim 5 of the '473 patent is invalid pursuant to 35 U.S.C. § 103 because it would have been obvious to a POSA as of September 2003, in view of the prior art.

For the reasons discussed below, the evidence presented at trial is clear and convincing that a POSA would have been motivated to inhibit c-Met to treat cancer; selected Kirin Example 5 as

a lead compound; and modified the compound to arrive at cabozantinib, with a reasonable expectation of obtaining a c-Met inhibitor.

1. A POSA would have been motivated to develop a c-Met tyrosine kinase inhibitor to treat cancer.

As of September 2003, researchers were excited about the prospects for gene-based cancer therapies targeting specific genetic alterations. The prior art taught that knowledge of these molecular defects allowed researchers to develop targeted therapies for treating cancer. FOF ¶ 17; Mega Tr. at 520:22–521:5; DTX-66.1 (Oliff). More specifically, it was known that defective or aberrant tyrosine kinases caused various cancers. FOF ¶ 18; Mega Tr. at 522:11–13.

It was known by September 2003 that inhibiting tyrosine kinases could treat a variety of cancers. And many pharmaceutical companies, including some of the largest and most sophisticated ones in the world, were developing tyrosine kinase inhibitors ("TKIs") to treat cancer. FOF ¶ 20; George Tr. at 591:6–11 (Q. "Now, a person of ordinary skill in the art, as of September 2003, would have understood that some of the largest and most sophisticated pharmaceutical companies in the world were investigating tyrosine kinase inhibitors; right?" A. "That's true."); MacMillan Tr. at 730:11–14 (Q. "By September of 2003, Dr. MacMillan, it's true that there were many companies pursuing tyrosine kinase inhibitors as cancer therapeutics; right?" A. "That's right."); DTX-17.3 at Table 2 (Traxler).

By September 2003, multiple TKIs that inhibited different tyrosine kinases and treated different cancers were not only in development, but had received approval, including in the United States. The first such approval came in 2001, when the FDA approved the TKI Gleevec to treat chronic myelogenous leukemia. FOF ¶ 22; George Tr. at 591:19–25. On cross-examination, Plaintiff's expert Dr. George agreed that the approval of Gleevec was an exciting time in the medical field, because it was the first time there was clinical evidence of successfully treating a

cancer by targeting a specific defective tyrosine kinase. George Tr. at 592:6–13. In fact, *Time* magazine featured the approval of Gleevec on its cover in 2001:

See DDX(Mega)-16.

Other TKIs received approval as cancer treatments shortly thereafter, George Tr. at 592:18–21, and a number of other TKIs were in development before the priority date. For example, by September 2003, Herceptin had been approved to treat breast cancer. George Tr. at 564:17–20. Other small-molecule TKIs, including Iressa and Tarceva, had been approved to treat cancer, or were in phase III clinical trials as of the 2003 publication of the prior art Traxler paper. DTX-17.3 at Table 2 (Traxler); George Tr. at 565:24–566:7.

It is also undisputed that the success of these early TKIs would have motivated a POSA to develop new therapies that targeted different tyrosine kinases, as stated in the 2002 Shawver prior art reference: "Generated by the success of Gleevec and Herceptin, the impetus for development of new targeted therapeutics that hold some promise as targets in cancer therapy extends to [tyrosine kinases] beyond HER2/neu, EGFR, and VEGFR2." DTX-39.5 (Shawver); *see also* FOF ¶ 54; George Tr. at 598:24-599:13; Mega Tr. at 527:12–528:5. Plaintiff's expert Dr. George further agreed that Gleevec's success motivated researchers to research the use of TKIs to treat

other cancers. George Tr. at 592:14–17 (Q. "And the success of Gleevec showed enthusiasm and motivation to do more research with tyrosine kinase inhibitors in other cancer settings; right?" A. "Yes, it did.").

One of those other tyrosine kinases generating interest in the field of cancer research was c-Met, which the parties agree "was a known receptor at the time." George Tr. at 593: 17–20; *see also* Mega Tr. at 528:8–22. MSN presented conclusive evidence that a POSA would have been motivated to pursue a c-Met inhibitor, Mega Tr. at 529:3–17, and Plaintiff's expert agreed at trial. George Tr. at 594:17–19 (Q. "So, as of September 2003, Doctor, there was motivation to pursue c-Met inhibitors; yes or no?" A. "Yes.").

The prior art also contains substantial discussion of c-Met inhibition that would have encouraged a POSA to pursue a c-Met inhibitor to treat cancer. Below is a summary of some of the prior art establishing this motivation that was discussed at trial:

- ***Shawver*** (DTX-39): disclosed c-Met as a "[n]ew target" that it is "expressed by cancer cells of various origin" and that "[c]linically, HGF/Met overexpression has been shown to correlate with poor prognosis in several types of cancer." DTX-39.5; George Tr. at 599:18–600:7, 600:20–22;
- ***Traxler*** (DTX-17): disclosed c-Met as one of the "[t]argets under evaluation in drug discovery projects" for the treatment of renal cancer in humans (DTX-17.2; DTX-17.2 at Table 1; FOF at ¶ 47; Mega Tr. 526:22–527:10; MacMillan Tr. at 732:7–9; George Tr. at 596:5–18), and that c-Met's "overexpression has been described in several cancer types and seems to correlate with cancer progression, metastasis and poor prognosis." DTX-17.13; George Tr. at 568:10–19 (c-Met is "overexpressed in several cancer types" and "seems to have an association or correlation with cancer progression metastasis and

prognosis in that there are activating mutations that have been described with the Met gene in some cancers.");

- ***Maulik*** (DTX-37): disclosed that c-Met inhibitors "have drawn much interest" (DTX-37.15), and that c-Met was "an attractive target for molecularly targeted therapy in a variety of solid tumors and hematological malignancies and designs of small molecule inhibitors and antibodies against c-Met would be clinically useful." DTX-37.16; FOF ¶¶ 49, 51; Mega Tr. at 528:8–25, 529:3–10; George Tr. at 602:7–11, 603:20–604:9.

In addition to these disclosures in the prior art, the Kirin Publication disclosed specific small molecule inhibitors of c-Met, including potent c-Met inhibitors with potent antitumor activity. Lepore Tr. at 428:22–430:9; McMillan Tr. at 675:18–21, 732:19–733:6; *See also* DTX-6.4 (the Kirin Publication); FOF ¶ 52. The Kirin Publication also disclosed that these compounds and compositions could be "used in the treatment of malignant tumors," including renal cancer. DTX.6.71 (the Kirin Publication).

Based on the disclosures in the prior art, a POSA would have been motivated and it would have been obvious for a POSA to pursue a c-Met inhibitor to treat cancer. Whether or not a POSA would have also been motivated to pursue TKIs targeting other tyrosine kinases in addition to c-Met is inconsequential for the Court's analysis. "[O]bviousness, 'does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away.'" *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1319 (Fed. Cir. 2017) (quoting *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014)); *Merck & Co., v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) ("That the '813 patent discloses a multitude [> 1,200] of effective combinations does not render any particular formulation less obvious.").

For example, in *Pfizer, Inc. v. Apotex, Inc.*, the Federal Circuit held that a POSA would have favorably considered benzene sulphonate, a known anion, and that its known acid strength, solubility, and other known chemical characteristics would have provided a POSA ample motivation to use benzene sulphonate in preparing a pharmaceutically acceptable salt, despite the fact that 52 other anions were known, and benzene sulphonate was only used in 0.25% of FDA-approved drugs. 480 F.3d 1348, 1362 (Fed. Cir. 2007). Similarly, in *Trustees of Columbia Univ*, the Federal Circuit rejected the patentee's argument that because "other scientists allegedly … cho[]se to pursue" alternatives, that there was no motivation to pursue the claimed invention. *Trustees of Columbia Univ. in City of New York v. Illumina, Inc*., 842 F. App'x 619, 625 (Fed. Cir. 2021) (citing *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012)). The Federal Circuit explained that "while it may be true that other scientists ultimately chose to research alternative[s]," "just because better alternatives exist in the prior art does not mean that an inferior alternative is inapt for obviousness purposes." *Id.*

Further, the evidence established that there was no "teaching away" from pursuing a c-Met inhibitor, which would require that the teaching "criticize, discredit, or otherwise discourage" the claimed solution. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731,739 (Fed. Cir. 2013). Plaintiff's experts agreed the prior art did not discourage targeting c-Met or testing c-Met inhibitors as potential cancer therapy. George Tr. at 606:3–7 (Q. "in looking at the prior art in this case, Dr. George, you've not found any reference that discouraged or disparaged the use of c-Met inhibition as a way to treat cancer, right?" A. "That's correct."); MacMillan Tr. at 733:7–11 (same). To the contrary, the art taught that c-Met was a promising target. *See, e.g.,* FOF ¶¶ 47-51.

For these reasons, there is no dispute that a POSA would have been amply motivated to develop a TKI targeting c-Met in order to treat cancer.

2. A POSA would have been aware of the benefits of developing an irreversible TKI.

As of September 2003, a POSA would have been aware of the benefits of developing an irreversible TKI. It was known that drugs may inhibit their biological targets reversibly or irreversibly. FOF ¶ 39; Lepore Tr. at 419:10–17; MacMillan Tr. at 712:23–713:19. When an irreversible inhibitor binds to its target, it forms a covalent bond with the target and inhibits it in a permanent way. FOF ¶ 39; Lepore Tr. at 419:10–420:24; MacMillan Tr. at 712:23–713:19. When a reversible inhibitor binds to its target, it can come off the target, and thus the inhibition would not be permanent. FOF ¶ 39; Lepore Tr. at 419:10-420:24; MacMillan Tr. at 712:23–713:19.

The prior art disclosed several advantages of irreversible inhibitors. FOF ¶ 40; Lepore Tr. at 4210:25–421:3. For example, the Silverman textbook taught that smaller and fewer doses were often needed to achieve the same effect when using irreversible inhibitors compared to reversible inhibitors. FOF ¶ 40; Lepore Tr. at 421:4–23; DTX-13.194 (Silverman). The Fry publication taught multiple potential advantages of irreversible TKIs, including "lowering the minimal plasma concentration at which activity occurs, minimizing multiple dosing requirements and eliminating the requirement for long plasma half-lives . . . [and] reduc[ing] toxicity due to any nonspecific interactions that may occur at high or prolonged plasma levels." DTX-30.5 (Fry); FOF ¶ 43; Lepore Tr. at 421:24–422:24, 424:6–13.

Dr. MacMillan agreed that a POSA would have understood that developing an irreversible inhibitor would be "wonderful." MacMillan Tr. at 731:15–20; FOF ¶ 41. For these reasons, there is no dispute about the desirability of an irreversible inhibitor or that a POSA would have been motivated to pursue an irreversible inhibitor in order to increase the efficacy of the inhibitor.

3. A POSA researching c-Met would have relied on the Kirin Publication to identify a lead compound.

The evidence at trial established that a POSA following the motivation in the art to pursue a c-Met inhibitor to treat cancer would have chosen a lead compound from the Kirin Publication. The parties do not dispute this point. Dr. MacMillan agreed on cross-examination that a POSA motivated to pursue a c-Met inhibiting compound would have started with the Kirin Publication. MacMillan Tr. at 735:10–13; *see also* Lepore Tr. at 431:1–5; FOF ¶ 56. That is because the Kirin Publication is the *only* prior art reference that disclosed specific exemplified small-molecule c-Met inhibiting compounds. FOF ¶ 56; Lepore Tr. at 430:20–25, 470:18–471:8; MacMillan Tr. at 735:5–9 (Q. "Dr. MacMillan, it's true, isn't it, that Kirin is the only prior art reference that you have identified in this case that discloses small-molecule c-Met inhibiting compounds; right?" A. "Yes."). Further, on cross examination, Dr. George agreed that a POSA would have been motivated to determine whether the Kirin Publication compounds could be used to treat cancer. George Tr. at 605:22–606:2 (Q. "So, as of September 2003, you agree, don't you, that a person of ordinary skill in the art would have been motivated to investigate whether the compounds disclosed in Kirin could be used as a treatment for cancer, you agree with that; don't you?" A. "Yes.").

In short, there is no dispute that the starting point for a POSA motivated to develop a small molecule c-Met inhibitor would have been the Kirin Publication.

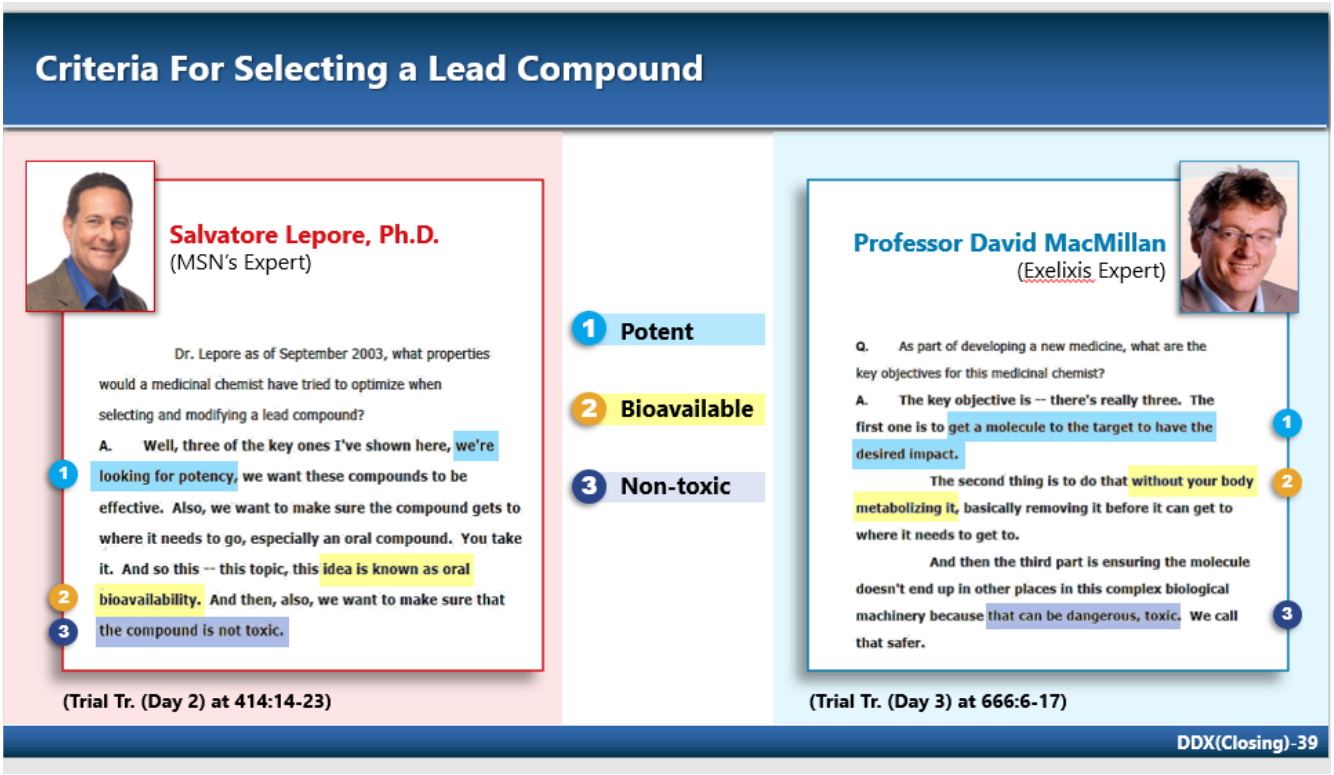
4. Kirin Example 5 would have been an obvious choice as a lead compound.

A POSA relying on the Kirin Publication would have identified Kirin Example 5 as the most promising lead compound, because it had the best mix of the desirable properties a medicinal chemist would have been looking for in drug development. A lead compound analysis should be "guided by evidence of the compound's pertinent properties," including activity and potency,

toxicity, and other relevant characteristics. *Otsuka*, 678 F.3d at 1292. That is precisely the analysis presented by MSN.

The lead compound analysis "must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound," rather, the analysis "requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art." *Daiichi Sankyo*, 619 F.3d at 1354. For example, selection of a lead compound may be obvious if it is one of a finite number of compounds identified in the prior art; it is one of the more "potent" compounds identified in the prior art; and/or the prior art disclosing the lead compound was ripe for further experimentation. *See, e.g., Altana Pharma*, 566 F.3d at 1007-09. For the reasons discussed below, the Court should similarly find Kirin Example 5 an obvious lead compound in this case.

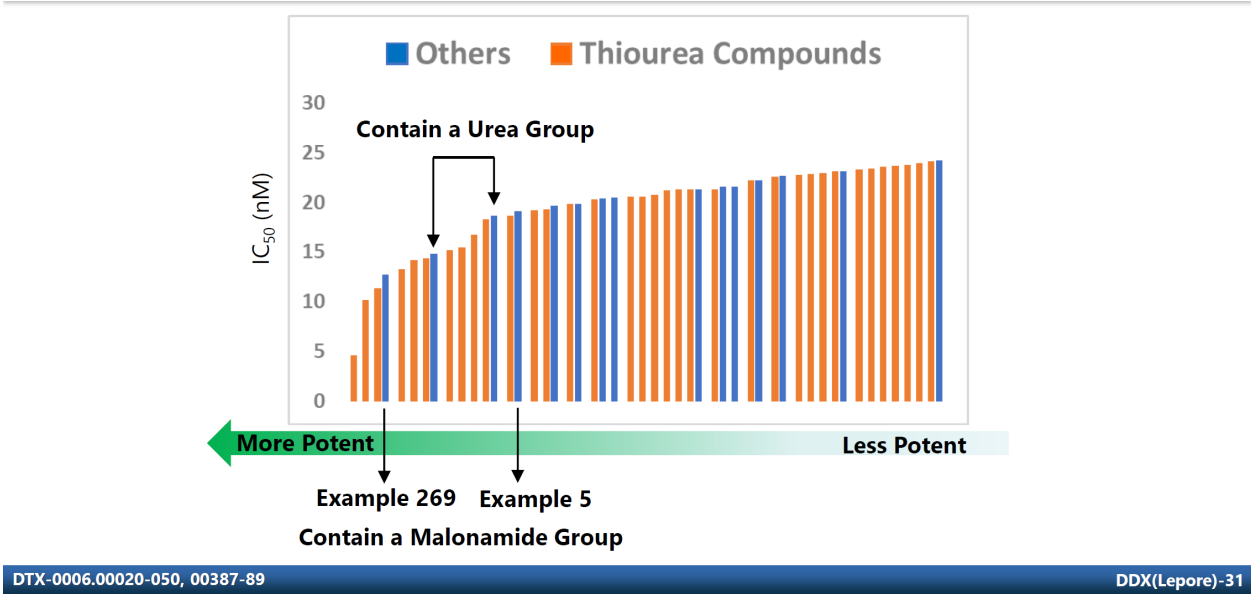
Both Dr. Lepore and Dr. MacMillan agreed that potency, bioavailability, and toxicity are properties that a medicinal chemist would have considered in selecting a lead compound. MacMillan Tr. at 666:4–15 (discussing potency, bioavailability, and toxicity), 725:15–23 (discussing potency); Lepore Tr. at 414:14–23 (discussing potency, bioavailability, and toxicity), 432:12–18 (discussing potency); FOF ¶ 30. The following demonstrative from MSN's closing argument illustrates the agreement between the parties' medicinal chemist experts:



See DDX(Closing)-39.

A POSA would have started by evaluating the Kirin Publication compounds for potency. To do so, they would have looked to the IC_{50} values[1] the Kirin Publication provides for the 333 exemplary compounds in Table 2. Lepore Tr. at 431:1–17; MacMillan Tr. at 725:9–23. A POSA would have evaluated the most potent compounds disclosed in Kirin as shown in the following demonstrative exhibit presented by Dr. Lepore:

[1] It is undisputed that a POSA would have measured a compound's potency by determining the concentration at which the compound inhibits 50% of the target, i.e., the compound's IC_{50} value. FOF ¶ 31; Lepore Tr. at 415:1–14; McMillan Tr. at 666:22–667:2.



See DDX(Lepore)-31.

After determining the most potent compounds, the POSA would have understood that the three most potent compounds in Table 2 were thiourea compounds. Lepore Tr. at 433:9–19; *See* DDX(Lepore)-24. The POSA would have further understood that thiourea compounds were known to have serious toxicity concerns. FOF ¶ 60; Lepore Tr. at 433:9–434:3, 436:22–437:11, 505:2–9. For example, the 1999 Onderwater prior art disclosed that, among other concerns, some "[t]hiourea-containing compounds" . . . "are pulmonary toxins or hepatotoxins." DTX-19.1 (Onderwater 1999).

A POSA also would have been concerned about the potential for toxicity. This concern would have motivated a POSA to deprioritize the thiourea compounds because of known toxicity concerns with these compounds. Lepore Tr. at 437:12-20 ("a POSA [] would have had concerns. They would have thought that [the Kirin Publication thiourea compounds] may have had toxicity issues. So they would have been deprioritized in terms of comping up with [] a lead compound"); MacMillan Tr. at 743:9–18; DTX-19.1 (Onderwater 1999); DTX-18.2 (Onderwater 1998).

After deprioritizing the thioureas, the next most potent non-thiourea compound (and the fourth most potent compound overall) is Kirin Example 269, which is a malonamide. FOF ¶¶ 66–67; Lepore Tr. at 437:21–438:5; MacMillan Tr. at 747:2–7. In evaluating Kirin Example 269, the POSA would have understood that it had good potency and the potential to be an irreversible inhibitor (a trait shared among malonamides), but would have further understood that it did not have a desirable oral bioavailability profile based on the well-known and highly influential Lipinski criteria.[2] FOF ¶¶ 67–69; Lepore Tr. at 438:6–439:10; MacMillan Tr. at 753:25–754:5 (admitting that a POSA would have recognized that the molecular weight of Kirin Example 269 was well over the Lipinski limit). In comparison, Kirin Example 5, which had similar potency to Kirin Example 269, with IC_{50} values of 12.5 and 18.9 nM, respectively, would have been predicted to be more orally bioavailable. FOF ¶ 72; Lepore Tr. at 439:12–25, 441:5–16. Thus, a POSA would have been motivated to prioritize Kirin Example 5 over Kirin Example 269, because it was predicted to have better oral bioavailability, which is one of the key characteristics analyzed in drug development of an oral drug. DTX.20; Lepore Tr. at 439:12–25 ("Kirin Example 5 would have been predicted to be more promising in terms of its oral bioavailability.").

While there were two exemplary non-thiourea compounds that had comparable, but slightly higher, potency to Kirin Example 5, those two compounds were urea compounds. FOF ¶¶ 70–71; Lepore Tr. at 438:25–439:11; DTX-6.20–50 (the Kirin Publication); DTX-6.387–89. A POSA would have known that urea compounds did not provide an opportunity for irreversible

[2] In 1997, Dr. Lipinski, a scientist at Pfizer, identified factors to evaluate the oral bioavailability of drugs under development. FOF ¶¶ 33–37; Lepore Tr. at 418:4–13; DTX-20.7 (Lipinski). Kirin Example 5 met the Lipinski criteria for all factors, but Kirin Example 269 exceeded the threshold for molecular weight, and was at the very upper limit of the threshold for Log P. Lepore Tr. at 439:12–25 (explaining that Kirin Example 5 "was Lipinski friendly" as it did not exceed "the criteria that Lipinski had set out."), 438:6–24 (explaining that Kirin Example 269 "didn't really fit with what we call the Lipinski criteria").

inhibition, and thus would have prioritized Kirin Example 5 over the two slightly more potent urea compounds in light of its potential to be an irreversible inhibitor, a highly desirable characteristic. FOF ¶ 71; Lepore Tr. at 438:25–439:11.

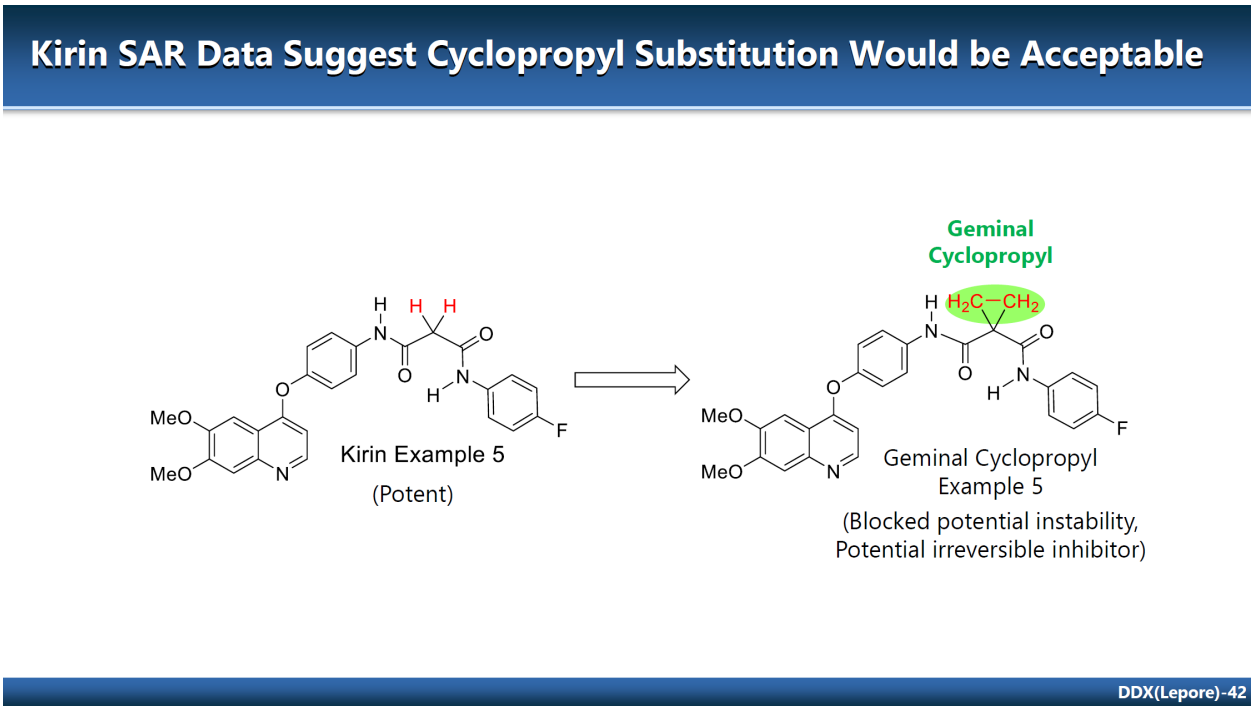
While Dr. MacMillan noted that cabozantinib was ultimately found not to be an irreversible inhibitor, that fact is irrelevant to a POSA's obviousness analysis as of the priority date. As discussed above in Section III.A.2, there is no dispute between the parties that a POSA would have known that an irreversible inhibitor would be desirable to increase the efficacy of the inhibitor. Further, Dr. Lepore testified that irreversible binding requires a "molecular hook" on the target (c-Met) *and* a counterpart on the compound. Lepore Tr. at 419:18–420:3. Plaintiff did not present any evidence to the contrary. Before September 2003, a POSA did not know whether c-Met contained an appropriately positioned "molecular hook" to guarantee irreversible inhibition. *Id*. at 463:2–8, 495:16–19. Nevertheless, given the undisputed advantageous properties of irreversible inhibitors, a POSA would have been motivated to select a lead compound that could provide the opportunity for irreversible inhibition (i.e., Kirin Example 5), with a reasonable expectation of obtaining an irreversible inhibitor in case c-Met contained a "molecular hook." *Id*. at 462:13–463:8.

In short, a POSA would have recognized that Kirin Example 5 was an obvious choice for a lead compound for further development, with an optimal mix of characteristics.

5. A POSA would have been motivated to modify Kirin Example 5 by incorporating a geminal-cyclopropyl ring into the malonamide group and would have had a reasonable expectation that the resulting compound would inhibit c-Met.

The evidence at trial showed that once a POSA had selected Kirin Example 5 as a lead compound, they would have been motivated to make a single modification by adding a geminal-cyclopropyl ring on the malonamide to improve the compound's metabolic stability and to increase

the potential for irreversible inhibition. A POSA would have understood that the geminal-cyclopropyl ring was the smallest ring that could be added to the molecule to replace the two hydrogen atoms of the middle carbon, which would have provided the POSA with a reasonable expectation that the new, more stable compound would inhibit c-Met.



See DDX(Lepore)-42.

The motivation to modify the lead compound "may come from any number of sources and need not necessarily be explicit in the prior art." *Otsuka*, 678 F.3d at 1292. The "pertinent properties guide the analysis" in this step as well. *Id.*; *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) ("The 'reason or motivation' need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old.") (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990)); *see also KSR*,

550 U.S. at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

There is no dispute that while Kirin Example 5 was disclosed as a potent inhibitor of c-Met based on the teaching of the Kirin Publication, it also had the potential for metabolic instability in one of its rare forms. Lepore Tr. at 441:25–442:18; *see also* DTX-23.2 (Williams) (teaching the equilibrium constant for the conversion of the stable form to the potentially unstable form is approximately 4×10^{-10}). Dr. MacMillan agreed that a POSA would have understood that Kirin Example 5 had the potential to be metabolically unstable and that a POSA would have wanted to make more stable compounds:

> Q. I think you said during your direct, Dr. MacMillan, that a POSA would have understood that the potential for Kirin Example 5 to be metabolically unstable; is that right?
> A. Yes.
> Q. And that was one of the areas where you and Dr. Lepore agreed; right?
> A. Correct.
> Q. Okay. And you agree, also, don't you, Dr. MacMillan, that a person of ordinary skill in the art as of September of – as of September of 2003 would have – would have hoped to be able to make more stable compounds than less stable compounds?
> A. Yeah, sure. Well, we don't want to make less stable compounds, but, yeah, they want to make more stable compounds.

MacMillan Tr. at 758:13–759:3.[3] Thus, Drs. Lepore and MacMillan agreed that a POSA would have been motivated to address the potential metabolic instability issue of Kirin Example 5.

[3] Two of the named inventors of the '473 patent, Lynne Bannen and Larry Mann, both of whom qualify as persons of at least ordinary skill in the art, explained that it was known in the art that an unsubstituted malonamide carbon could be unstable. Bannen Tr. at 262:24–263:9 ("An

A POSA would have been motivated to address the potential metabolic instability of Kirin Example 5 by replacing the two hydrogen atoms with a geminal cyclopropyl group for at least two reasons: 1) a cyclopropyl ring is the smallest substituent that could be added to address Kirin Example 5's potential metabolic instability consistent with the Lipinski criteria; and 2) a cyclopropyl ring would have created a potentially irreversible inhibitor.

On the first point, as Dr. Lepore testified, the POSA would have been guided by Lipinski's Rule of 5 when modifying Kirin Example 5. Lepore Tr. at 442:25–443:7. A POSA would have chosen a group that does not add hydrogen bond donors or hydrogen bond acceptors, and a small group that does not unduly increase the molecular weight of the compound. Lepore Tr. at 443:8–24. These considerations would have led a POSA to replace the two hydrogens with two carbons connected to each other with a bond, thus forming a geminal cyclopropyl group. *Id.*; *see also* MacMillan Tr. at 760:24–761:1 (Q. "And I think you said that a cyclopropyl is the smallest ring that you can form; is that right?" A. "It is."). Further, a POSA would have reasonably expected that introducing a geminal cyclopropyl group would have addressed Kirin Example 5's potential instability issue. Lepore Tr. at 444:9–15, 449:4–9 (explaining that a POSA would have been motivated to incorporate a geminal cyclopropyl group into Kirin Example 5 "mainly as a blocking" group, to address the potential instability issue).[4]

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experienced medicinal chemist would be able to take an educated guess at potential areas of a molecule that might be more prone to oxidative metabolism than others."); Mann Tr. at 266:16–20 (Q. "And when you say hydrogens between two carbonyl groups are known to be acidic, was that known to any medicinal chemist[] in the field?" A. "That's taught in organic chemistry in sophomore year in undergraduate.").

[4] One the named inventors of the '473 patent, Lynne Bannen, explained that a senior medicinal chemist (a POSA), would have reasonably expected that introducing the geminal cyclopropyl into the malonamide linker of Kirin Example 5 would have eliminated the middle carbon in the malonamide group as a site of potential metabolic instability. Bannen Tr. at 263:13–20.

Second, Dr. Lepore also explained that a POSA would have found the cyclopropyl ring attractive because it "would have given to the molecule the potential for irreversible inhibition, and a POSA would have reasonably expected that by doing so, it would have resulted in a molecule that was still—had activity because of the data set present in the Kirin publication. They would have activity to inhibit the c-Met biological target." Lepore Tr. at 449:4–16; *see also* MacMillian Tr. at 731:15-20. Dr. Lepore testified that based on structure-activity relationship data in the Kirin Publication, "a POSA would have had an expectation that putting a cyclopropyl . . . would give the molecule — continue to give the molecule bioactivity." Lepore Tr. at 448:2–20; *see also* FOF ¶ 89. While Dr. MacMillan speculated that this substitution could reduce the potency of Example 5, he did not testify that a POSA would have expected this substitution to cause the molecule to stop inhibiting c-Met. FOF ¶ 90.

The prior art further taught cyclopropyl containing compounds that acted as irreversible inhibitors. For example, the Kelner prior art taught MGI 114, an illudin compound containing a cyclopropyl group, was in phase II clinical trial for treating solid tumors. DTX-27.1 (Kelner) at Abstract and Figure 1. The McMorris prior art taught a mechanism by which illudins irreversibly inhibited their biological targets. Lepore Tr. at 445:16–447:5; DTX-25.4 (McMorris) at Scheme 1. Dr. Lepore explained that a POSA would have understood that a geminal cyclopropyl analog of Kirin Example 5 could similarly irreversibly inhibit c-Met, assuming c-Met had a properly located nucleophile ("molecular hook"). Lepore Tr. at 447:6–16, 461:3–6.

Dr. Lepore summarized the dual motivation to modify Example 5 on direct examination:

> So a POSA would have been motivated to take Kirin Example 5 and incorporate a cyclopropyl ring mainly as a blocking, to avoid the potential instability issue. But it would also would have, as a secondary benefit, would have given to the molecule the potential for irreversible inhibition, and a POSA would have reasonably expected that

> by doing so, it would have resulted in a molecule that was still – had activity because of the data set present in the Kirin publication. They would have activity to inhibit the c-Met biological target.

See Lepore Tr. at 449:4–16.

The evidence at trial also established that a POSA would have been motivated to substitute the hydrogens with a cyclopropyl ring, as a POSA would have understood that because of their unique properties, cyclopropyls were of great interest to chemists and that this substitution could improve the antitumor properties of the compound. The prior art taught compounds containing a cyclopropyl ring were "of great general interest, particularly to synthetic organic chemists and to bioorganic chemists." DTX-28.2 (Salaün). Specifically, it taught that these compounds "are endowed with a large spectrum of biological properties ranging from enzyme inhibitions to antibiotic, antiviral, antitumor and neurochemical properties." *Id.* Dr. Lepore testified that a POSA would have found a cyclopropyl ring to be an attractive option. Lepore Tr. at 424:14–426:5 ("[The POSA] would have known that [cyclopropyl groups] are capable of acting in a variety of biological properties, including in tumor activity that would have been important and well-known moiety.").

Therefore, the evidence at trial established that a POSA would have been motivated to make a single modification to Kirin Example 5 by adding the geminal-cyclopropyl group, with a reasonable expectation of obtaining a c-Met inhibitor.

6. Plaintiff produced no persuasive evidence of secondary considerations.

At trial, Plaintiff attempted to show evidence of secondary indicia of nonobviousness to overcome MSN's prima facie showing of obviousness. Plaintiff's purported evidence of secondary considerations is not persuasive for several reasons.

a. Cabozantinib has not satisfied a long-felt, unmet need.

Plaintiff did not clearly identify the long-felt unmet need that cabozantinib allegedly met at trial. Dr. George testified that cabozantinib met a long-felt unmet need for improved therapy options over chemotherapy. George Tr. at 606:12–18. He also testified that cabozantinib met a long-felt unmet need for "new" or "more" options for treating RCC, HCC, and thyroid cancers. George Tr. at 572:24–573:21. But these vague, nonspecific allegations are legally insufficient, and factually unsupported. For example, Dr. George admitted that cabozantinib only fills a need for improved therapy options over chemotherapy "in part." George Tr. at 606:19–24; *see also id.* at 588:12–14 (testifying that some patients cannot tolerate Cabometyx). Thus, Plaintiff has not shown that cabozantinib satisfied a need for "improved therapy options over chemotherapy."

The trial record also established that while cabozantinib provided another treatment option for some renal, hepatocellular, and thyroid cancers, it was neither the first, nor the only, TKI available to treat these conditions. For example, the TKI pazopanib was approved to treat RCC prior to the approval of Cabometyx in 2016, which was originally approved as a second-line treatment. George Tr. at 612:23–613:7; D.I. 275-1 (Proposed Final Pretrial Order, Ex. 1 (Uncontested Facts)) at ¶¶ 53, 57. Axitinib and sorafenib, which are TKIs, and everolimus were also all available as second-line RCC treatments before Cabometyx was approved as a second-line treatment for RCC in 2016. George Tr. 613:8–17. When Cabometyx was approved as a second-line treatment for HCC in 2019 (D.I. 275-1 at ¶ 59), sorafenib had already been approved as a second-line HCC treatment for HCC. George Tr. at 613:21–614:1. Regorafenib was also approved as a second-line HCC treatment prior to Cabometyx. George Tr. at 614:2–6. Similarly, when Cabometyx received approval for the treatment of DTC in 2021 (D.I. 275-1 at ¶ 61), lenvatinib and sorafenib were already both approved to treat DTC. George Tr. 614:10–18. Finally,

vandetanib was already available to treat MTC (*id.* at 614:24–615:5) when Cometriq was approved to treat it in 2012. D.I. 275-1 at ¶¶ 62, 65.

Further, it is undisputed that there is still a need for new, additional, and improved treatment options for treating RCC, HCC, and thyroid cancers. George Tr. at 611:10–13, 612:15–17, 542:21–543:3, 543:9–16, 543:25–544:6; Mega Tr. at 795:10–19, 795:20–796:11, 797:16–23, 798:14–20; *see also* FOF ¶¶ 99–107. Thus, cabozantinib has not satisfied a long-felt unmet need for "new" or "more" options for treating these cancers.

b. Plaintiff has not shown any failure of others to synthesize cabozantinib

Plaintiff has not shown any failure of others to synthesize the compound of claim 5 of the '473 patent. Actual evidence of failure of others must be shown, as "the mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004). Dr. George admitted that he did not identify any instance where someone failed to synthesize the compound of claim 5 of the '473 patent. George Tr. 616:6–11. Dr. George also admitted that he did not know why the compounds disclosed in the Kirin Publication did not advance to market. *Id.* at 615:24–616:5.

c. Plaintiff has not shown commercial success.

At trial, Plaintiff attempted to present evidence that Cabometyx (which contains cabozantinib as the active ingredient) is a commercial success. Tate Tr. at 631:13–17. For the reasons explained below, Plaintiff failed to present evidence supporting this conclusion.

Commercial success may be relevant "because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Plaintiff's expert, Michael Tate, agreed. Tate Tr. at 649:23–650:4.

However, as MSN's expert, Dr. McDuff testified, Mr. Tate's conclusion that Cabometyx is a commercial success was not supported by any analysis addressing the core question of whether others would have developed a product sooner in response to market forces. McDuff Tr. at 770:10–21. Specifically, Mr. Tate's analysis (i) lacked "comparisons to other products," (ii) lacked "evaluation of commercialization costs to bring the product to market," and (iii) relied on "uninformative market shares." McDuff Tr. at 770:22–771:4, 771:8–772:12; DTX-231.3. Therefore, Plaintiff did not show that the cabozantinib products were a commercial success.

d. Plaintiff has not shown any unexpected results.

Plaintiff also has not demonstrated the claimed invention of claim 5, cabozantinib or a pharmaceutically acceptable salt thereof, was associated with any unexpected results. To demonstrate unexpected results, Plaintiff must compare the relevant properties of cabozantinib to the relevant properties of the closest prior art. "[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Koa Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006); *see also Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014).

Dr. George admitted that he did not conduct any such comparison. For example, Dr. George admitted that he has not compared the inhibition profile of Kirin Example 5—or any compounds in the Kirin Publication, for that matter—to the inhibition profile of cabozantinib. George Tr. at 615:17–23. Therefore, Plaintiff has not demonstrated unexpected results.

e. Simultaneous invention

Plaintiff did not offer any evidence to rebut MSN's evidence that the simultaneous invention of the prior art compounds in the Kirin Publication, including Example 5, is objective evidence of obviousness. *See* Lepore Tr. at 451:24–452:10. "Simultaneous invention is evidence

that one of ordinary skill in the art would have considered it obvious to combine elements of the prior art." *Warner Chilcott Co. v. Teva Pharm. USA, Inc.*, 37 F. Supp. 3d 731, 739 (D. Del. 2014) (citing *Nat'l Steel Car, Ltd v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1338 (Fed. Cir. 2004)).

The simultaneous invention of other structurally similar c-Met inhibiting compounds that had potent antitumor activities shows that the synthesis of such compounds was well within the skills of the POSA as "[t]he fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art." *Int'l Glass Co. v. U.S.*, 408 F.2d 395, 405 (Ct. Cl. 1969); *Trustees of Columbia Univ.*, 620 F. App'x 916 at 930; *Spectrum Pharm., Inc. v. Sandoz Inc.*, No. 2:12-cv-111, 2015 WL 794674, *14 (D. Nev. Feb. 25, 2015), *aff'd*, 802 F.3d 1326, 1335 (Fed. Cir. 2015).

In short, taking all four *Graham* factors into account, MSN provided clear and convincing evidence at trial that all asserted claims would have been obvious.

IV. CONCLUSION

Claim 5 of the of the '473 patent is invalid because it would have been obvious to a POSA as of September 2003. The Court should invalidate claim 5 and enter judgment for MSN and against Plaintiff.

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